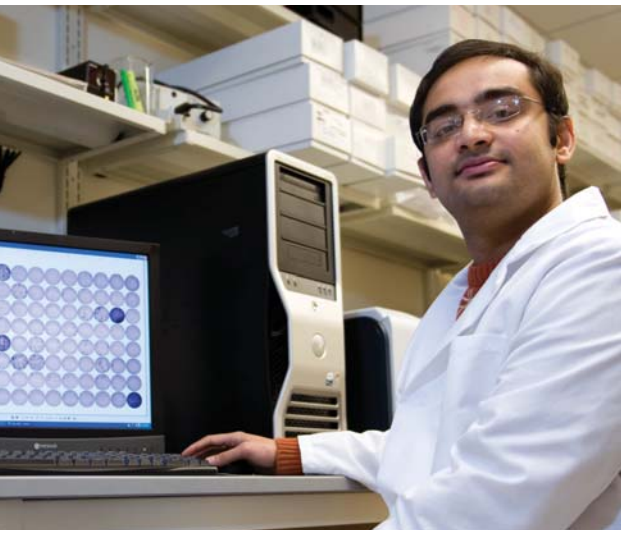
# Viral Pathogenesis

**Norman L. Letvin, MD, Chief**

Sarah Schaake

**The Division of Viral Pathogenesis is a research division that focuses on elucidating the pathogenesis of AIDS and related opportunistic infections, and exploring novel strategies to vaccinate for protection against HIV-1 infections.**



Harikrishnan Balachandran

## 2009–2010 HIGHLIGHTS

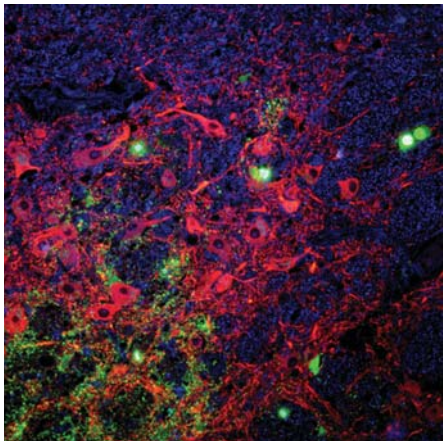
Among the many recent advances made by investigators in the Division, the Letvin laboratory has shown that a gene known as TRIM5 exerts substantial control over the level of AIDS virus replication in rhesus monkeys and affects long term clinical consequences of the infection. This observation highlights the importance of genetic characteristics in the outcome of HIV-1 infections. The lab has also shown that vaccination with a novel configuration of synthetic gene products, known as "mosaics," can generate immune responses in monkeys that recognize a genetically diverse population of HIV-1 isolates. This finding suggests a strategy for dealing through vaccination with the extreme genetic diversity of HIV-1 isolates infecting humans.

In studies of why an AIDS virus infection causes disease in Asian monkeys but not in African monkeys, the Schmitz laboratory has shown that elimination of immune responses against the virus

does not result in the development of disease in African monkeys. This observation underscores the importance of nonimmune mechanisms in the development of AIDS in HIV-1-infected humans.

The Koralnik laboratory has shown that JCV, the virus that causes Progressive Multifocal Leukoencephalopathy (PML) in humans, infects not only the glial cells in the central nervous system white matter as previously thought, but also infects granule cell neurons in the cerebellum and cortical pyramidal cells in the gray matter of the brain. These newly described infections are both associated clinically with symptomatic brain inflammation.

Finally, the Permar laboratory has shown that vaccination can generate robust immune responses in the breast milk of lactating monkeys, suggesting that vaccination may prove a viable approach to decreasing mother-to-child transmission of HIV-1 during the period of breast feeding.



Productive infection of glial cells by JC virus in the midbrain of an immunosuppressed patient with Progressive Multifocal Leukoencephalopathy (Christian Wuethrich, PhD)

## SELECTED PUBLICATIONS


Lim SY, Rogers T, Chan T, Whitney JB, Kim J, Sodroski J, Letvin NL. TRIM5alpha modulates immunodeficiency virus control in rhesus monkey. *PLoS Pathog* 2010; 6:e10000738.

Santra S, Liao HX, Zhang R, Muldoon M, Watson S, Fischer W, Theiler J, Szinger J, Balachandran H, Buzby A, Quinn D, Parks RJ, Tsao CY, Carville A, Mansfield KG, Pavlakis GN, Felber BK, Haynes BF, Korber BT, Letvin NL. Mosaic vaccines elicit CD8+ T lymphocyte responses that confer enhanced immune coverage of diverse HIV strains in monkeys. *Nat Med* 2010; 16:324-8.

Zahn RC, Rett MD, Li M, Tang H, Korioth-Schmitz B, Balachandran H, White R, Pryputniewicz S, Letvin NL, Kaur A, Montefiori DC, Carville A, Hirsch VM, Allan JS, Schmitz JE. Suppression of adaptive immune responses during primary SIV infection of sabaeus African green monkeys delays a partial containment of viremia but does not induce disease. *Blood* 2010; 115(15):3070-8.

Chen Y, Bord E, Tompkins T, Miller J, Tan CS, Kinkel RP, Stein MC, Viscidi R, Ngo LH, Koralnik IJ. Asymptomatic reactivation of JC virus in patients treated with natalizumab. *N Engl J Med* 2009; 361:1067-74.

Wilks AB, Christian EC, Seaman MS, Sircar P, Carville A, Gomez CE, Esteban M, Pantaleo G, Barouch DH, Letvin NL, Permar SR. Robust vaccine-elicited cellular immune responses in breast milk following systemic simian immunodeficiency virus DNA prime and live virus vector boost vaccination of lactating rhesus monkeys. *J Immunol* 2010; 185:7097-106.


## HONORS AND AWARDS

**Keith Reimann, DVM's** laboratory has recently received a 7 year contract from the NIH to support the continued generation of monoclonal antibodies that can alter immune responses of the rhesus monkey for studying novel therapeutics for use in organ transplantation.

**Norman Letvin, MD's** laboratory continues to receive funding from the NIH-funded Center for HIV AIDS Vaccine Immunology and the Gates Foundation for work on novel strategies for HIV vaccination.

## FACULTY

**Mohammed Asmal, MD, PhD**

**Raphael Dolin, MD**

**Igor J. Koralnik, MD**

**Norman L. Letvin, MD**

**Sallie R. Permar, MD, PhD**

**Keith A. Reimann, DVM**

**Sampa Santra, PhD**

**Joern E. Schmitz, MD, PhD**

**Michael S. Seaman, PhD**

**Xinzhen Yang, PhD**

**Wendy W. Yeh, MD**

## RESEARCH FUNDING

| | Direct | Indirect |
|---|---|---|
| Federal | 10,662,873 | 5,250,692 |
| Non Federal | 3,270,107 | 252,771 |